PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 843	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IL2004/000921	International filing date *(day/month/year)* 05.10.2004	Priority date *(day/month/year)* 07.10.2003
International Patent Classification (IPC) or national classification and IPC C07K16/40, A61K39/395, A61P37/00, C07K16/00		
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.04.2005	25.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer van Klompenburg, W Telephone No. +31 70 340-2243

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2004/000921

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-13, 15-25, 27-79	as originally filed

Claims, Numbers

1-85	as originally filed

Drawings, Sheets

1/9-9/9	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2004/000921

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 59-61,70-81

because:

☒ the said international application, or the said claims Nos. 70-81 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 59-61

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 4-6,14-16,21-29,32-34,42-44,50-52,59-61,67-69,72-74 (completely) and claims 1-3, 7-13,17-20,30,31,35-41,45-49,53-58,62-66,70,71,75-85 (partially) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-13,17-20,30-40,45-48,53-57,62-69,82-85
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-58,62-69,82-85
Industrial applicability (IA)	Yes:	Claims	1-69,82-85
	No:	Claims	70-81

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 70-81 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

This Authority considers that there are 18 inventions covered by the claims indicated as follows:

Invention 1 Claims :1,3,7-13,17-20,30,36-40,45-48,53-57,62-65,70,75-85 (all partially)
A preparation comprising one or more antibodies being capable of binding to SEQ ID NO:1. A method of preparing a monoclonal antibody. An antibody, a monoclonal antibody, a pharmaceutical composition. A method of regulating a biochemical activity of a NIK molecule. A composition of matter comprising a substrate covalently attached to a polypeptide of SEQ ID NO:1. The use of a preparation comprising an antibody recognizing SEQ ID NO:1 in the manufacture of a medicament. A method of treatment. A method for purification of a NIK binding protein. The use of an antibody for an ELISA assay and the usr of an antibody for immune purification of NIK.

Invention 2-6: Claims 1,3,7-13,17-20,30,36-40,45-48,53-57,62-65,70,75-85 (all partially)
As invention 1, but whereby invention 2 is characterized by SEQ ID NO:2, invention 3 by SEQ ID NO:3 etc.

Invention 7 Claims: 4,14-16,21,24,27,32,42,50,67,72 completely,
1-3,7-13,17-20,30,31,35-41,45-49,53-58,62-66,70,71,75-85(partially)
As invention1, but characterized by SEQ ID NO:7 and additionaly hybidoma clone No-I-3092 and monoclonal antibodies genereted by it.

Invention 8-18

As defined and (as far as applicable) for inventions 1-7, but whereby each of the inventions is characterized By SEQ ID NO: 8-13,15,18,19,20,22, such that invention 8 is characterized by SEQ ID NO:8, invention 9 by SEQ ID NO:9 etc.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

Antibodies to NIK are known see for example Chen et al. Oncogene (2003) Vol. 22, pp. 4348-4355 (D1). Antibodies to NIK are also cited in the present application as belonging to the prior art (Table 2)
D1 discloses (fig.4) antibodies to NIK which are used in a western blot.

In the light of the abovementioned prior art document D1, the problem underlying the invention is regarded to be the provision of further antibodies against NIK. The 18 solutions as described and claimed in the current application can be summarized as the provision of antibodies to 18 fragments of NIK (including SEQ iD NO:22, full length NIK).

In view of the fact that antibodies against NIK and their use are known, due to the essential differences in structures and function of the NIK fragments, and since no other special technical feature, common to this problem and its solutions could be distinguished,In conclusion, the groups of claims are not linked by common or corresponding special technical features and define 18 different inventions not linked by a single general inventive concept.
The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.
This communication is limited to the subject matter of the inventions for which the corresponding fees were paid, namely inventions 1,7,11 and 12 as defined above and corresponding to SEQ ID NOs: 1,7,11,12.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability of the first invention; citations and explanations supporting such statement

Reference is made to the following documents:

D1: CHEN DANYING ET AL: "NIK is a component of the EGF/heregulin receptor signaling complexes." ONCOGENE. 10 JUL 2003, vol. 22, no. 28, 10 July 2003 (2003-07-10), pages 4348-4355, XP002315069 ISSN: 0950-9232

D2: US-A-5 854 003 (ROTHE MIKE ET AL) 29 December 1998 (1998-12-29)
D3: WO 97/37016 A (BOLDIN MARK ; METT IGOR (IL); WALLACH DAVID (IL); MALININ NIKOLAI (IL)) 9 October 1997 (1997-10-09)
D4: WO 03/087380 A (RAMAKRISHNAN PARAMESWARAN ; SHMUSHKOVICH TAISIA (IL); WALLACH DAVID (I) 23 October 2003 (2003-10-23)
D5: US-A-5 030 565 (NIMAN ET AL) 9 July 1991 (1991-07-09)
D6: WO 95/26365 A (UNITED BIOMEDICAL, INC; WANG, CHANG, YI) 5 October 1995 (1995-10-05)
D7: WO 90/10231 A (REPLICO MEDICAL AB) 7 September 1990 (1990-09-07)

1 Invention 1 (SEQ ID NO:1)

Inventive Step (Art. 33(3) PCT

1.1 Preparations comprising antibodies reactive to nuclear factor kappa B inducing kinase (NIK) are known from various sources (D1 and present application, Table 2). D1 is regarded as the closest prior art, it discloses NIK antibodies succesfully used in Western-blotting (figure 4, panel C). Claim 1 differs from D1 in that the antibody recognize the NIK fragment represented by SEQ ID NO: 1. There seems no technical effect to be related to this difference. The problem is therefore regarded to be the provision of further NIK antibodies. The solution as described in independent claim is the provision of an anti-NIK antibody recognizing SEQ ID NO:1. This solution however cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons. The subject-matter of claim 1 consists in the selection of a fragment from the range of the known NIK protein sequence. Such a selection can only be regarded as inventive, if the selected fragment presents unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claim 1.

1.2 The same reasoning applies mutatis mutandis to independent claims 17,18,19,30,39,48,57,65 all relating to SEQ ID NO:1. These claims therefore also lack inventive step (Art. 33(3) PCT).

1.3 Dependent claims 3,7-13,19,20,36-38,40,45-47,53-56,62-64 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step with respect to the prior art named in the present ptoceedings. The reasons therefor are that the additional features of the said dependent claims are a combination of features obvious to the skilled person in consideration of

documents D1-D3, or they concern minor modifications which lie within the normal practice of the skilled person.

2 Invention 7 (SEQ ID NO:7)

2.1 Novelty (Art. 33(2) PCT)

D5 Concerns monoclonal antibodies raised against a peptide with 4 amino acid identical to SEQ ID NO:7. The target seems not to be related to NIK. Nevertheless due to the wording of claim 1 of the present application, namely "or a portion of said amino acid sequence", claim 1 is not novel over D5. The same applies for claims 2,5,7,8,30,31,33,35-37,59,65,66,68,84.

2.2 Inventive Step (Art. 33(3) PCT)

Next to lacking novelty due to claiming antibodies binding to " a portion" of the respective amino acid sequences, the above claims also lack inventive step for the same reasons as detailed in section 1.1-1.3 for invention 1.

3 Invention 11 (SEQ ID NO:11)

3.1 Novelty (Art. 33(2) PCT)

D6 Concerns monoclonal antibodies raised against a peptide (SEQ ID NO: 38) with 4 amino acid identical to SEQ ID NO:11. The target of these monoclonal antibodies is the CH4 domain of the epsilon chain of human IgE and is not to related to NIK. Nevertheless due to the wording of claim 1 of the present application, namely "or a portion of said amino acid sequence", claim 1 is not novel over D5. The same applies for claims 2,4,7,8,30-32,35-37,60,65-67,84.

3.2 Inventive Step (Art. 33(3) PCT)

Next to lacking novelty due to claiming antibodies binding to " a portion" of the respective amino acid sequences, the above claims also lack inventive step for the same reasons as detailed in section 1.1-1.3 for invention 1.

4 Invention 12 (SEQ ID NO:12)

4.1 Novelty (Art. 33(2) PCT)

D7 Concerns antibodies specific for a peptide(claim 2, HTLV-1 gag 337-355) with 4 amino acids identical to SEQ ID NO:12. The target is not related to NIK. Nevertheless due

to the wording of claim 1 of the present application, namely "or a portion of said amino acid sequence", claim 1 is not novel over D5. The same applies for claims 2,5,7,8,30,31,33,35-37,61,65,66,68,84.

4.2 Inventive Step (Art. 33(3) PCT)

Next to lacking novelty due to claiming antibodies binding to " a portion" of the respective amino acid sequences, the above claims also lack inventive step for the same reasons as detailed in section 1.1-1.3 for invention 1.

Re Item VI

Certain documents cited

The following published document casts doubts on the validity of the claim to priority of the present application:

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03087380	23-10-2003	15-04-2003	18-04-2002